Use of gangliosides and pharmaceutical formulation containing same

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Inventor(s):
Applicant(s): IOSA DANIEL JESUS [AR] +
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Abstract of **BE 1006598 (A6)**

The present invention relates to a pharmaceutical formulation which issuitable for the treatment of optic neuritis, optic nerve atrophy, opticdemyelinisation and genital herpes virus infection and any other viralinfection (such as AIDS), characterised in that it comprises, as an activeingredient, a ganglioside. or physiologically acceptable salts or esters ofsaid ganglioside, with a pharmaceutical vehicle or excipient.

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Use of gangliosides and composition pharmaceuti- that by containing Background of the invention
It is considered that the mixture of gangliosides made up of glycosphingolipides containing sialic acid, natural and highly purified, that one finds in abundance in the plasmatic membranes, play of the substantial roles in the functions of the membranes, in particular in the nervous cells, like those of the cardiac system of conduction, which quantitatively contains more gangliosides (three times more) that the myocardium (1) and qualitatively different of those of the myocardium (1) ordinary.

An highly purified preparation of gangliosides mixed, extracted from brains the bovine ones, is bringing on the market by pharmaceutical companies, like Fidia SpA, stalemate. Arg. 234.528, Italy or Laboratories Beta of Argentina (EP-A-44717903075. 2-insulation of gangliosides, deposited on November 7, 1990 and EP-A-91310220. 8 - Method of obtaining of purified GM1, deposited on November 5, 1991). The preparation process was validated in order to exclude any possible contamination by slow viruses (prions) (2) and gives reproducible preparations with different proportions in the composition of the four gangliosides natural the most used: GM1, GDIa, GDIb and GTIb. The first, GM1, are also

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available single in concentrations going up to 100 mg per ampoule. The mixture of the four gangliosides mentioned must be managed by the intramuscular path, while the preparation of GM1 can be managed by intramuscular or intravenous path.

The pharmacology of a mixture of four gangliosides, on the peripheral and autonomous nervous system, was studied in several animal species. It is substantial to emphasize that its administration is deprived of toxic effects (3).

The effectiveness of the gangliosides was established by seekers as well in the field of the experimental neuropathies as clinical (4-5).

The gangliosides exert, in vitro, an activity substantial neuroprotectrice by preventing the induced excessive stimulating by the presence of concentrations raised out of exciting amino acids (6).

Gangliosides and nerves: models of experimental animals
The first study of gangliosodes during an experimental nervous dysfonction was realized on the cat after interruption surgical of fibres pre-and post-ganglionic of the nerve leading to the membrane nictitante or flashing in order to allow the study as well cholinergic system as adrenergic. The electrical stimulation after surgery did not induce the normal contraction, but, in the weeks which followed, there was restoration of incomplete, but progressive contraction. This is supposed to be due to the formation of new neuronic connections to the body terminal. The action of the gangliosides was obvious after to have caused lesions of the two fibre types, suggesting a general action on the nervous regeneration (7).

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This being in memory, of many seekers have

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tested gangliosides during studies in vivo and in vitro, in order to show if these substances (gangliosides mixed or single GM1) were capable to standardize disorders of the nervous system.

In mice db/db, one noted that the catecholamine levels were reduced in several bodies, particularly the heart (8-9). The administration of gangliosides brought back these rates to normal (9). The regeneration of the nervous function requires an efficient transport system axonic. The gangliosides revealed that they repaired the failures of ATPase activity in the nerve induced diabetic sciatic nerve with AI (10) and that they corrected the metabolic activities faded in the nerves sciatics nerve of induced diabetic rats to the streptozocine (11).

Gangliosides at the man
The gangliosides make proof of beneficial effects after damages traumatic, toxic and metabolic and one published a passage in review of their action in the peripheral neuropathy (12).

A study also showed the beneficial effect of the gangliosides on the autonomous nervous ordering of the bladder in diabetic patients (13).

There are clinical proofs of recovering improved with a treatment by ganglioside GM1 of the damages undergone by the central nervous system (14). Moreover, the application of mixtures of gangliosides for the treatment of certain ocular complaints, like the neurite rétrobulbaire and Nerves Paulsy, was already proposed (12).

The cardioneuropathy of Chagas, recognized by the World Health Organization like component one of the most substantial causes of congestive cardiac failure and dead sudden in the world, appears

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by disorders of the nervous system autonomous, digestive and cardiovascular (15). Pathological alterations in the nervous plexuses is the main characteristic of the disease. Patients with all the degrees of chronic stage of the disease have faulty homeostatic mechanisms in response with a change of posture, expressing a failure with a raising reflex of the systemic vascular resistance, probably like consequence of a damage of the inervation postganglionnaire sympathetic nerve of vessels of resistance (1).

The plasmatic concentration in norepinephrine is also faded in the chronic disease of Chagas and was regarded as component a mark of progressive dysautonomy by Daniel Iosa (16). This is why, on of the fact that the cardioneuropathy of Chagas is basically a disease of the nervous system, Daniel Iosa quoted above proposed and showed that the treatment by gangliosides was capable to improve the function of the autonomous nervous system, initially during an open test and later during a test controlled by placebo, stochastic, into double blind, realized according to regulations' of Food and Drug Administration of the E. U. A. (17-1).

It is substantial to point out that until the moment when D. Iosa published its exposed relative with the disease of Chagas, one did not have any treatment for the cardioneuropathy of Chagas and it was the first relationship of a sure and effective medicament for the treatment of the disease (1).

The optical neurite is an inflammatory process affecting the optical nerve which can be secondary with a viral disease, démyélinisante, or autoimmune. The typical clinical table ranges between 15 and 45 years and includes/understands an acute loss of vision associated with a pain rétrobulbaire, a painful sensitivity with

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pressure or with palpation and a pain at the time of the eye movements. These symptoms can be less serious when they are seen with an acute neurite rétrobulbaire. The examination reveals a pupillary defect afférant relative, usually in the form of a central scotome or sécocentral, the head of the optical nerve is typically swollen of oedema of the layer of nervous fibres surrounding. On the contrary, the neurite rétrobulbaire has a disc appearing normal during the acute episode. Visual recovering primer usually after 7 days and a total recovering application of the weeks even of the months. However, of the studies showed that 50 to 80% patients make the experiment of a certain degree of optical atrophy and all the patients after develop a defect of the layer of nervous fibres detectable an episode of neurite optical acute. The patients with neurite optical secondary with an autoimmune disease, although clinically presenting a similar clinical table at those described higher, tend to being suceptibles to suffer from an irreversible visual loss. The establishment of the initial diagnosis must include/understand a complete blood counting, a sedimentation rate of the erythrocytes, a test of antinuclear antibodies, a test serologic complémen- to conceal for syphilis (VDRL), a radiography of the chest and visual fields formal to detect entities specifically manageable. The patients of which the state after does not improve 10 to 14 days must undergo a scanner CT with high resolution of the brain and orbits or an imagery by magnetic resonance, a neurological consultation with lumbar puncture and a medical consultation. Actual therapy: systemic.

The use of corticosteroids for the treatment of the neurite optical residence contreversé. Trôlées studies idiot did not make it possible to show any

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difference of the state long-term patients suffering of neurite optical and treated by pharmacological amounts of systemic corticosteroids. Since any entity which compresses the optical nerve (i.e. inflammatory aneurysmes, tumors, masses) can simulate the clinical table noted with an optical neurite, it is of cardinal importance to remove these conditions, especially because they can also initially answer systemic corticosteroids with strong amount. Moreover, the therapy by steroids is not inoffensive. Reactions prejudicial with the systemic corticosteroids were reported at 16,9% hospitalized and consecutively supervised patients.

A daily treatment by systemic corticosteroids can be complicated by multiple potentially serious secondary effects, including the formation of a cataract, a superinfection, an electrolytic imbalance, a leucocytose, an gastro-intestinal bleeding, an acute psychosis, an aseptic necrosis of the bones, a hypertension and an hyperglycemia.

These secondary effects can produce a considerable and same morbidity a strong mortality. (taken in: Optic Neuritis: Thomas C. Spoor, Geoffrey Kwitko and John Ramocki, in Current Ocular Therapy (3), Fraunfelder F., Hampton Roy F. and Martha Meyer Editors, W. B. Saunders Company, 1990, Hardcourt Bruce Jovanovich, Inc., Philadelphia, London, Toronto, Montreal, Sydney, Tokyo.

Genital herpes, our venereal disease most substantial: taken in American Newspaper off Obstretrics and gynecology 1979,135 n5,553-554, by Hermann L. Gardner, Mr. D.

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1) the frequency of the genital herpes among the private patients exceeds the combined frequency of all the other main venereal diseases.

2) The genital herpes once acquired, remains in the victim until its dead and is always subject with reactivation in the form of a contagious recurring infection.

3) No satisfying treatment is available, neither for the primary phase, nor for the recurring phases, that it either with curative titre or that it or as symptomatic relief.

4) One does not have any method of effective control logical epidemic; one does not have until present any found immunologic vaccine and the transmission is possible apart from the presence of subjective symptoms or visible lesions of the outer one.

5) Serious sexual problems appear frequently with the genital herpes, in particular when the two partners make the expérince frequent repetitions.

6) The perinatal effects on the children can be catastrophic. The extent of the damage caused by this disease on the total human population was not determined but is probably great with that suspectée.

7) The genital herpes is inseparably linked of a certain manner to the development of a cancer of the collar of the uterus.

8) Gonorrhoea, the syphilis and the majority of the other conventional diseases sexually transmissible are now readily curable, a fact which decreases their relative importance when one compares them with the genital herpes.

Actual treatment: deduced from a test of cream containing topical 3,0% of edoxudine for the treatment of the herpes

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genital recurring, test carried out in a Canadian multiple hospital center, clinically started, controlled by placebo, into double blind, stochastic, put at the point by Stephen Sacks, Lorne Tyrell and David Lawee and Al Tea Newspaper off Infectious Diseases Flight. 164, p. 665- 678-1991.

Now, the acyclovir by oral route is the single treatment authorized for an infection with recurring genital herpes. In the clinically started study, the acyclovir by oral route has reduced viral overflowing, although the durations of the present lesions were not decreased by an active treatment. The effects of the acyclovir on the lesions and viral overflowing were more apparent when the treatment was started in the patient on signs forerunners. However, the reduction of the organic symptoms was not substantial. The use intermittent, episodical, of acyclovir by oral route is at the same time less effective and less prefered by patients than a chronic suppression. The topical administration of acyclovir does not constitute an effective treatment of the recurring genital herpes.

The invention
With all the given aforementioned ones and the experiment on the treatment by gangliosides of Daniel Iosa, one conceived experiments based on the application of monogangliosides and one carried them out on assigned patients of ocular diseases like an optical neurite, an atrophy of the optical nerve, an optical demyelinisation, etc and one carried out experiments with mixed gangliosides for an infection with virus of the genital herpes, the presbyopia and related disorders of reduced visual activity.

It is substantial to note that all the treatments were carried out with the assent of the patients, in

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tuning with the principles of the declaration of Helsinki.

Brief description of the invention
The invention thus has as an object the use of gangliosides for the clothes industry of a pharmaceutical composition intended for the suffering treatment of patient of neurite optical, atrophy of optical nerves, optical demyelinisation, presbyopia and disorders of the reduced visual acuity related, as well as infection with virus of the genital herpes.

The invention also has as an object the use of the ganglioside mentioned GMI for the clothes industry of a pharmaceutical composition intended for the suffering treatment of patient of neurite optical, atropie of optical nerves or optical demyelinisation.

The invention still has as an object the use of a mixture of gangliosides for the clothes industry of a pharmaceutical composition intended for the suffering treatment of patient of an infection with virus of the genital herpes.

The present invention finally has as an object a pharmaceutical composition which is appropriate for the treatment of the optical neurite, of the atrophy of the optical nerve, the optical demyelinisation and an infection with virus of the genital herpes and any other viral infection (like the AIDS), characterized in what it includes/understands, as active ingredient, a ganglioside, or salts or physiologically acceptable esters of this ganglioside, with a vehicle or excipient pharmaceutical.

Detailed description of the invention
With fine of the present invention, the pharmaceutical administration of gangliosides and their physiologically acceptable salts are carried out by the path relationship rail (for example, by subcutaneous, intravenous path

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or intramuscular), by the rectal path, vaginal and also transdermal, however that the gangliosides or their salts are incorporated with conventional preparations, that it is in solid or liquid form, optionally in combination with other active ingredients, presented in a suitable form, for example of the suppositories, solutions, suspensions or emulsions. As examples of suspension mediums or nonaqueous solvents, one can quote the propylene glycol, polyethylene glycol, vegetal oils, as the oil of olive and organic esters injectable, like oleate of ethyl, of derived from paraffin, etc

These compositions can also include/understand an adjuvant, like a wetting agent, dispersive and emulsive, solubilizing agents and/or stabilisers for the regulating of the osmotic pressure and/or the regulators of the pH. Those can be sterilized, for example, by filtration through a filter retaining the bacteria, by incorporation of sterilizing agents to the composition, or by irradiation. One can also manufacture the compositions in the form of solid preparations sterile, which one can dissolve in sterile water, or in any other sterile injectable medium, immediately before employment.

In the case of suppositories, one can present the gangliosides in suspensions or fat emulsions, by resorting to the use of greases, wax, natural or hydrogenated oils, etc

One can preferably present the compositions in accordance with the invention in the form of unitary amounts, each unitary amount serving required an attached amount of ganglioside. The daily amount varies conveniently from 40 to 100 mg managed in the form of several unitary amounts. An unitary amount will contain it conveniently

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or gangliosides in a proportion from 40 to 100 mg and more. According to the nature and body weight of the patient to be treated and/or gravity of the disease, like also of the period pendent which the administration takes place, it can however be necessary to deviate of the aforementioned amounts.

The optimum amount and the type of administration of the gangliosides which are necessary in each case can be readily determined by the specialists in the technical one.

Specific compositions of the present invention prepare, of a manner in oneself known in the pharmaceutical art (see Remington' S Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, for a description of the preparation of composition of this kind).

For treatment of the genital herpes or any other viral infection, in accordance with the present invention, the effectiveness of the active ingredient does not depend on a specific ganglioside. The practical use of the invention revealed that infections caused by the virus of the genital herpes, like also certain disorders of the visual activity (presbyopie, for example), could be treated by mixtures of gangliosides.

In the particular case of other optical diseases, like an optical neurite, an atrophy of the optical nerve and a demyelinisation of the optical, the aforementioned nerve practical proved to be only beneficial only if GM1 is used, or a derivative of the internal ester type of this one, or a pharmaceutically acceptable salt of this monoganglioside or a derivative of the internal ester type of this one. It is substantial to point out that, like one has it already indicated, of the interesting mixed gangliosides for the treatment of the optical neurite révé-

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lèrent not to be interesting in the case reported here.

GM1, managed by the intramuscular or intravenous path, is sure and effective for the treatment of the optical neurite, the optical atrophy and the optical demyelinisation.

It is substantial to point out that the benefit of this treatment present step the else known toxic effect of the available therapy by corticosteroids and that my exposed led to the first relationship in the world of a blind person suffering of neurite optical with demyelinisation and atrophies optical, which found the vision.

The application of mixtures of gangliosides, or gangliosides individual, as active ingredients for the treatment of the aforementioned diseases, is described in the examples which follow and which are given only with fine the purely illustrative ones.

Example 1 assigned Treatment of a patient of neurite optical clinical History G. Mr. R. : 7276 of Dr. Daniel Iosa Private Center of Medicine, authorized by the Ministry for the Public Health of Cordoba in Argentina.

May 27, 1992:
A woman, age: 42 years, weight: 70 kg, cut: 1,76 m, Argentina; specialist in medicine paediatric, came to consult me for blindness bilateral (except for the light and of the index) which led it to cease its professional working and to prevent it from going single in city, or same to carry out single things, like the preparation of a meal for its family. It told me that it had attended a conference which I had given concerning the reinervation of an patient chagasic and it wished to know if I could make

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something for it. It was accompanied by her husband, also doctor of medicine, which me said that one had diagnosed at his wife an optical neurite with bilateral demyelinisation of the optical nerves and atrophies optical nerves.

The patient was in perfect state of health until April 1990, moment from which it started to undergo an acute loss of visual acuity and consulted six different specialists in ophthalmology, who proceeded to different studies and diagnosed: neurite optical, bilateral demyelinisation of the optical nerves, atrophies bilateral optical nerves. It was treated by high amounts of corticosteroids without any improvement, seeing its visual acuity worsening each day and suffering aforementioned secondary effects of this therapy: formation of cataract on the straight eye which had to be operated and hypertension.

It was also treated by mixed gangliosides, its worsening state each day during the treatment (see claim relative with the use of gangliosides mixed in the neurite rétrobulbaire).

With the first visit that it made me, it complained about sensitivity to an intense bilateral ocular pain, of sensation of burn and blindness, except for the light and of the index.

Physical examination: Arterial blood pressure 150/80
Retina: typical diagnosis of bilateral atrophy of the nerves opti- ques.

Visual acuity: only for the light and the index
All other examinations: normal with the ex- ception of the operation previously mentioned relative with the formation

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of a cataract on the straight eye.

I managed propranolol at a rate of 40 mg per day with the patient to treat his moderate hypertension, however that I sent it towards other specialists to confirm my diagnosis. Two other specialists in ophthalmology confirmed the incurable character of the disease and the diagnosis of demyelinisation and bilateral optical atrophy. The clinical anamnèse patients was the following one: April 9, 1990: visual acuity decreased by acute manner and intense céphalalgies examination of the visual acuity: straight eye: 1/10 left eye: 9/10 January 23, 1991: pseudofaguia of the straight eye, Pa holds suffers from céphalalgies and ocular pains.

(Prof. specialist NR: 13116) February 6, 1991: straight eye: 1/10 left eye: 4/10 February 28, 1991: straight eye: 2/10 left eye: 4/10 (Prof. specialist NR: 5106) June 4, 1991: the patient is view by a member of the French company of

ophtalomology and a member of Society off Eye Surgeons and American Academy off Ophthalmology: (Prof. specialist NR: 11900).

The specialist asked: a) an electroretinogram: dicotomy and desinchronisation (July 5, 1991) b) électrooculogramme: normal (July 22, 1991) D) evoked visual potential: July 5, 1991

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straight eye: 16 P100: 112,35 msec (5,92 rV) left eye: 16 P100: 115,29 msec (6,04 rV)
Conclusion: delayed myelenic conduction in the two optical paths with left prevalence E) retina: atrophy bilateral optical nerves: July 5, 1991.

May 21, 1992: the patient was vuepar another spécialis- you who found: visual acuity: straight eye: 20/400 (Snel- len) left eye: 2/200
Diagnosis: atrophy bilateral optical nerves
Treatment: no, because of the défail- lance of the treatment by corticosteroids prior.

September 1, 1992: the patient was examines by another specialist, who found:
Visual acuity straight eye: index to 30 cm
Left visual acuity eye: index to 30 cm
Chromatic vision: dyschromatopsie: tests of Ishihara for chromatic blindness: of 24 plates
Stereo test: Stereo Optical C. Inc. Chica- go, the patient cannot see any the animals (rabbit, cat, écureil, monkey, cock)
September 4, 1992: the patient signed the assent with information and began the treatment with
GM1, 100 mg per day by injection intramus- culaire.

September 18, 1992: the patient expressed that it saw better and that the pain in the two eyes had completely disappeared. The physical examination

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was negative, blood pressure 130/80 September 21, 1992: ophthalmological evaluating: the patient could walk single and it saw again
Visual acuity: straight eye: 20/400 left eye: 20/400
Test of Ishihara: it could see. nth from the sixth plate and 8.16 and 17.

Stereo test: it could see the cock in A and rabbit out of B. It could not see out of C.

A retinography was recommended.

September 22, 1992: the patient said whom it could go single pendent the night period.

It felt and seemed happy.

Visual acuity: straight eye: 20/200 left eye: 20/200
Chromatic vision: 1,11, 16,17 Stéréopsie: 1,2, 3, normal animals: normal October 7, 1992: evoked visual potential: bilateral normal (P100) October 9, 1992: the patient sees each day better (this as well with regard to the brought closer vision as distant) December 2, 1992: fine of 60 ampoules of treatment by
GM1
Visual acuity: bilateral 20/100
The patient was capable to read again, to work in her house, was capable to help her son for her school duties in residence, to walk single with a complete safety. It did not suffer any more a any ocular pain, nor of its céphalalgies

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daily terrible.

Example 2
Treatment of the genital herpes or any other viral infection (other than Herpes zoster or zoster about which one already spoke), like also of presbyopia or of disorders of the visual acuity reported.

Exposed treatment and ratio of the case Patient: Mr. C. G. anamnèse clinical of the private Center of Medicine 7248. EMI17.1

Patient: age: 52 years, weight: 82 kg and size: 1, 86 m.

Profession: specialist in saving and elevated position in the government. Phd.

March 9, 1992: the patient came to my cabinet to complain about:
1) Genital herpes with 30 years evolution with monthly recurrences (it was treated by gamma globulins, iduléa, acyclovir (by drinks oral and cream without any beneficial effect, it suffered from intense pains to each repetition.

2) Presbyopia: bifocal glasses: straight eye: + 050 D left eye: + 125 D
The patient began the treatment with mixed gangliosides, receiving 60 ampoules of 40 mg per pendent day 60 days.

December 16, 1992: the patient indicated that it did not suffer

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more repetitions of the genital herpes and a new ophthalmological examination tuellement revealed the same day that presbyopia was not nonalone does not lie extent, like that product habi-, but bine rather than it had highly decreased, the new evaluating values being the following ones: straight eye: 000 left eye: + 050D.

The exposed mentioned one, I can conclude that a pharmaceutical preparation containing an effective proportion from a mixture of gangliosides (GM1, GDIa, GDIb and GTIb), managed by intramuscular injections are interesting for the treatment of an infection with virus of the genital herpes (other than the Zoster herpes), like also for the treatment of

presbyopia and other reported visual disorders.

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Result Page

Claims 1. Pharmaceutical composition suitable with the suffering treatment of patient of an infection with virus of the genital herpes, neurite optical, atrophy of optical nerves, demyelinisation optical and disorders of the reduced visual acuity related, comprising physiologically acceptable gangliosides or salts or esters of those, as active ingredients in association with a vehicle or excipient pharmaceutical.

2. Pharmaceutical composition following claim 1, suitable with the optical treatment of patient assigned of neurite, atrophy of optical nerves, optical demyelinisation and disorders of the reduced visual acuity related comprising, as active ingredients, physiologically acceptable monosialogangliosides (GM1) or salts or esters of those.

3. Pharmaceutical composition following claim 1 comprising as active ingredients, a mixture of gangliosides natural, including GM1, GDla, GDlb and GTlb or of physiologically acceptable salts or esters of those in a vehicle or excipient pharmaceutically acceptable suitable with the administration by the intramuscular or intravenous path.

4. Use of gangliosides or salts or physiologically acceptable esters of those for the clothes industry of a pharmaceutical composition intended for the suffering treatment of patient of neurite optical, atrophy of optical nerves, optical demyelinisation and disorders of the reduced visual acuity related.

5. Use of a monosialoganglioside (GM1) or its salts (GM1) or its salts or esters physiologically acceptable, for the clothes industry of a composition

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pharmaceutical intended for the suffering treatment of patient of neurite optical, atrophy of optical nerves and optical demylinisation.

6. Use of a mixture of gangliosides natural including GM1, GD1a, GDlb and GTlb or their physiologically acceptable salts or esters intended for the suffering treatment of patient of infections with virus of the genital herpes or other infections with virus, except for Herpes zoster.

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